

In re Application of:
Aizawa et al.
Serial No.: 09/830,019
Filed: September 21, 2001
Page 3

PATENT
Attorney Docket No. SHIM1120

Remarks

Claims 1-3 and 6-15 were pending prior to this Response, with claims 8-12, 14 and 15 having been withdrawn from further consideration pursuant to 37 C.F.R § 1.142(b). By the present communication, no claims have been added, claim 1 has been amended to define Applicants' invention with greater particularity, and claims 6 and 8-15 have been canceled without prejudice. The amendments do not raise any issues of new matter and the amended claims do not present new issues requiring further consideration or search. Support for amended claim 1 may be found, among others, at page 17, lines 33-35; and Example 1 of the specification. Accordingly, claims 1-3 and 7 are currently pending in this application.

Information Disclosure Statement

The Examiner alleges that the newly submitted Information Disclosure Statement fails to fully comply with 37 CFR 1.97. Applicants submit herewith a new IDS for further consideration with the RCE. Accordingly, entry and consideration of the IDS is respectfully requested.

Claim Objections

Applicants respectfully traverse the objection to claims 6 and 13 as allegedly being of improper dependent form for failing to further limit the subject matter of the previous claim. Applicants have canceled claims 6 and 13, rendering the objection moot. Accordingly, Applicants respectfully request withdrawal of the objection.

Rejection under 35 U.S.C. § 112, Second Paragraph

Applicants respectfully traverse the rejection of claims 1-3, 6-7 and 13 as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the Examiner alleges that it is unclear if claim 1 requires that the natural or attenuated toxin have a formalin molecule bound to a lysine residue of the toxin. Applicants have canceled claims 6 and 13, rendering the rejection moot as to those

claims. Applicants have amended claim 1 to clarify that a formalin molecule is bound to lysine residues of the “attenuated” toxin. As described in the specification, either natural or mutant toxins can be used as a starting material to produce the attenuated toxin. A natural toxin before attenuation treatment would retain serine residues (Ser), glutamic acid residues (Glu), and lysine residues (Lys) in its original position in the amino acid sequence. The present invention also requires a mutant toxin, which is to be subjected to attenuation treatment, to retain Ser, Glu and Lys of the natural toxin (please see page 7, lines 4-13; page 9, lines 28-34; and page 9, line 35 to page 10, line 5 of the specification). As is clear for one of skill in the art, the present invention’s attenuation treatment with formalin does not cause amino acid substitutions, deletions, insertions, or additions. Thus, natural/mutant toxins that originally retain Ser, Glu, and Lys would also keep these residues at their original position after formalin treatment. Furthermore, as clearly described at page 11, lines 28-31 of the specification, formalin treatment causes formalin molecules to attack the NH₂ group of Lys, thus forming a Schiff base at that site. Therefore, one of skill in the art could readily recognize that the formalin treatment on natural/mutant toxins that retain Ser, Glu, and Lys would result in attenuated toxins that (1) also retain Ser, Glu, and Lys at its original site in the amino acid sequence and (2) a formalin molecule is bound to the Lys of the attenuated toxins.

Accordingly, reconsideration and withdrawal of the rejection of claims under 35 U.S.C. § 112, second paragraph are respectfully requested.

Rejection under 35 U.S.C. § 102(b)

Applicants respectfully traverse the rejection of claims 1, 3, 6, 7 and 13 as allegedly anticipated by Esposito et al (hereinafter “Esposito”). Specifically, the Examiner indicates: “Esposito et al. teaches of an adjuvant comprising an attenuated toxin, specifically, an attenuated cholera toxin. Esposito et al. obtained the attenuated cholera toxin via chemical treatment of the natural toxin with formalin”. The Examiner concludes that Esposito teaches the claimed composition because “the adjuvant of Esposito et al. is structurally the same as the claimed invention . . . [and] is obtained via the same attenuation technique as instantly claimed”.

As described in Examples 1-2 of the instant specification, the present invention's adjuvant comprises an attenuated toxin that has been prepared by attenuating a *purified* toxin protein. Example 1 describes that the cholera toxin to be attenuated was prepared at the purity level of about "95%". In contrast, Esposito seems to have utilized "*crude*" cholera toxin to produce toxoid (for example, see p. 120, left column, first paragraph). Thus, Applicants submit that Esposito's toxoid obtained by treating "*crude*" cholera toxin is structurally different from the present invention's attenuated toxin in that Esposito's toxoid may contain proteins or other components in addition to the cholera toxin protein. To clarify this difference, Applicants have amended claim 1 to insert the limitation "*purified*." Support for the amended recitation can be found at page 17, lines 33-35, Example 1, among others in the specification.

The reactivity of formalin varies greatly depending on the types of proteins to be treated. Since Esposito utilized "*crude*" toxin, which is a mixture of cholera toxin and various other protein components, one skilled in the art could not recognize what protein component in the mixture has actually been modified via the formalin treatment. In other words, even if detoxification is achieved through formalin treatment on "*crude*" toxin, there still remains a possibility that some component other than cholera toxin has been modified to inhibit cholera toxin activity. Esposito not only fails to teach attenuation of "*purified*" cholera toxin, but also fails to disclose that the degree of detoxification of the crude toxoid reaches 1/2000 of natural cholera toxin.

Finally, Esposito discloses that an attenuated cholera toxin can be obtained via chemical treatment with formalin, and state that crude cholera toxin that is converted to toxoid by treatment with 0.2% formalin at 35°C for 4 days proved to be three to five times more *antigenic* in guinea pigs and rabbits than the parent toxin on an equivalent dose basis. Although Esposito teaches that formalin treatment can elevate the antigenicity (i.e., the capacity of an agent to stimulate the formation of specific antibodies to *itself*) of *crude* cholera toxin, the prior art neither teaches nor suggests the *adjuvant activity* of the purified and attenuated cholera toxin. Thus, the prior art's disclosure is limited to a crude toxoid that can act as a specific *antigen*, and therefore does not detect nor disclose adjuvant activity, that is, an activity to *enhance* production

In re Application of:
Aizawa et al.
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Page 6

PATENT
Attorney Docket No. SHIM1120

of an antibody specific to an antigen other than the adjuvant itself.

Anticipation under 35 U.S.C. § 102(b) requires that the reference recite each and every element of the claims in a single document. Since Esposito et al. fails to disclose each and every element of the invention adjuvant, as defined by amended claim 1, Applicants respectfully submit that the Examiner has failed to establish anticipation under 35 U.S.C. § 102 (b) over Esposito et al. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Conclusion

In summary, for the reasons set forth herein, Applicants maintain that claims 1-3 and 7 clearly and patentably define the invention and respectfully request that the Examiner withdraw all rejections and pass the application to allowance. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Enclosed is Check No. 580569 in the amount of \$3,130.00 consisting of \$790.00 for the Request for Continued Examination fee, \$2,160.00 for Five Month Extension of Time fee, and \$180.00 for the Information Disclosure Statement fee. The Commissioner is hereby authorized to charge any other fees that may be required by this paper or credit any overpayment to Deposit Account No. 07-1896.

Respectfully submitted,



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